Layout and/or size adjusted for ease of reading and printing.

74-3624-14 (Rev October 2002)

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Pharmacia &Upjohn

Current insert showing proposed Geriatric Use text.

R-Gene® 10

10% Arginine Hydrochloride Injection, USP For Intravenous Use

DESCRIPTION

Each 100 mL of R-Gene® 10 (10% Arginine Hydrochloride Injection, USP) for intravenous use contains 10 g of L-Arginine Hydrochloride, USP in Water for Injection, USP. L-arginine is a naturally occurring amino acid.

R-Gene® 10 is hypertonic (950 mOsmol/liter) and contains 47.5 mEq of chloride ion per 100 mL of solution. The pH is adjusted to 5.6 (5.0-6.5) with arginine base or hydrochloric acid.

CLINICAL PHARMACOLOGY

Intravenous infusion of R-Gene® 10 often induces a pronounced rise in the plasma level of human growth hormone (HGH) in subjects with intact pituitary function. This rise is usually diminished or absent in patients with impairment of this function.

Expected Plasma Levels of HGH in ng/mL

Patient	Control Range	Range of Peak Response to Arginine
Normal	0-6	10-30
Pituitary deficient	0-4	0-10

These ranges are based on the mean values of plasma HGH levels calculated from the data of several clinical investigators and reflect their experiences with various methods of radioimmunoassay. Upon gaining experience with this diagnostic test, each clinician will establish his/her own ranges for control and peak levels of HGH.

L-arginine is a normal metabolite in animals and man and has a low order of toxicity.

INDICATIONS AND USAGE

R-Gene® 10 is indicated as an intravenous stimulant to the pituitary for the release of human growth hormone in patients where the measurement of pituitary reserve for HGH can be of diagnostic usefulness. It can be used as a diagnostic aid in such conditions as panhypopituitarism, pituitary dwarfism, chromophobe adenoma, postsurgical craniopharyngioma, hypophysectomy, pituitary trauma, acromegaly, gigantism and problems of growth and stature.

If the insulin hypoglycemia test has indicated a deficiency of pituitary reserve for HGH, a test with R-Gene® 10 is advisable to confirm the negative

response. This can be done after a waiting period of one day. As patients may not respond to R-Gene® 10 (10% Arginine Hydrochloride Injection, USP) during the first test, the unresponsive patient should be tested again to confirm the negative result. A second test can be performed after a waiting period of one day. Some patients who respond to R-Gene® 10 do not respond to insulin and vice versa. The rate of false positive responses for R-Gene® 10 is approximately 32%, and the rate of false negatives is approximately 27%.

CONTRAINDICATIONS

The administration of R-Gene® 10 is contraindicated in persons having highly allergic tendencies.

WARNINGS

There have been two reports of possible overdosage of R-Gene® 10 in children. EXTREME CAUTION MUST BE EXERCISED WHEN INFUSING R-GENE® 10 INTO PEDIATRIC PATIENTS. OVERDOSAGE OF R-GENE® 10 IN PEDIATRIC PATIENTS CAN RESULT IN HYPERCHLOREMIC METABOLIC ACIDOSIS, CEREBRAL EDEMA, OR POSSIBLY DEATH.

R-Gene® 10 should always be administered by intravenous injection because of its hypertonicity.

A suitable antihistaminic drug should be available in the event that an allergic reaction occurs.

R-Gene® 10 is a diagnostic aid and is not intended for therapeutic use.

PRECAUTIONS

General

R-Gene® 10 is a hypertonic (950 mOsmol/liter) and acidic (average pH of 5.6) solution that can irritate tissues. Care should be used to insure administration of R-Gene® 10 through a patent catheter within a patent vein. Excessive rates of infusion may result in local irritation and in flushing, nausea, or vomiting. Inadequate dosing or prolongation of the infusion period may diminish the stimulus to the pituitary and nullify the test.

The arginine in R-Gene® 10 can be metabolized resulting in nitrogen-containing products for excretion. The effect of an acute amino acid or nitrogen burden upon patients with impairment of renal function should be considered when R-Gene® 10 is to be administered.

The chloride content of R-Gene® 10 is 47.5 mEq per 100 mL of solution, and the effect of infusing this amount of chloride into patients with electrolyte imbalance should be evaluated before the test is undertaken.

It should be noted that the basal and post stimulation levels of growth hormone are elevated in patients who are pregnant or are taking oral contraceptives.

Carcinogenesis, mutagenesis, and impairment of fertility

Long term animal studies have not been performed to evaluate the carcinogenic potential, the mutagenic potential or the effect on fertility of intravenously administered R-Gene® 10.

Pregnancy Category B

Reproduction studies have been performed in rabbits and mice at doses 12 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to R-Gene® 10 (10% Arginine Hydrochloride Injection, USP). There have been no adequate or well controlled studies for the use of R-Gene® 10 in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should not be used during pregnancy.

Nursing mothers: It is not known whether intravenous administration of R-Gene® 10 could result in significant quantities of arginine in breast milk. Systemically administered amino acids are secreted into breast milk in quantities not likely to have a deleterious effect on the infant. Nevertheless, caution should be exercised when R-Gene® 10 is to be administered to nursing women.

[Insert the following statement here:]

Geriatric Use
Clinical studies of arginine did not include a sufficient number of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

ADVERSE REACTIONS

Adverse reactions associated with 1670 infusions in premarketing studies were as follows:

Non-specific side effects consisting of nausea, vomiting, headache, flushing, numbness and local venous irritation were reported in approximately 3% of the patients.

One patient had an allergic reaction which was manifested as a confluent macular rash with reddening and swelling of the hands and face. The rash subsided rapidly after the infusion was terminated and 50 mg of diphenhydramine were administered. One patient had an apparent decrease in platelet count from 150,000 to 60,000. One patient with a history of acrocyanosis had an exacerbation of this condition following infusion of R-Gene® 10.

OVERDOSAGE

An overdosage may cause a transient metabolic acidosis with hyperventilation. The acidosis will be compensated and the base deficit will return to normal following completion of the infusion. If the condition persists, the deficit should be determined and corrected by a calculated dose of an alkalizing agent. See "WARNINGS" for information about overdosage in pediatric patients.

DOSAGE AND ADMINISTRATION

The intravenous dose for adults is 300 mL (30 g arginine hydrochloride) of R-Gene® 10. The intravenous dose for children is 5 mL (0.5 g arginine hydrochloride) per kilogram of body weight of R-Gene® 10.

The intravenous infusion of R-Gene® 10 is a part of the test for measurement of pituitary reserve of human growth hormone and, for successful administration of the test, clinical conditions and procedures should be as follows:

1. The test should be scheduled in the morning following a normal night's sleep, and an overnight fast should continue through the test period.
2. Patients must be placed at bed rest for at least 30

minutes before the infusion begins. Care should be taken to minimize apprehension and distress. This is particularly important in children.

3. R-Gene® 10 (10% Arginine Hydrochloride Injection, USP) should be infused through an indwelling needle or soft catheter placed in an antecubital vein or other suitable vein. Blood samples should be taken by venipuncture from the contra-lateral arm.
4. A desirable schedule for drawing blood samples is at −30, 0, 30, 60, 90, 120 and 150 minutes.
5. R-Gene® 10 should be infused beginning at zero time at a uniform rate which will permit the recommended dose to be administered in 30 minutes.
6. Blood samples should be promptly centrifuged and the plasma stored at −20°C until assayed by one of the published radioimmunoassay procedures.
7. Diagnostic test results showing a deficiency of pituitary reserve for HGH should be confirmed by a second test with R-Gene® 10, or one may elect to confirm with the insulin hypoglycemia test. A waiting period of one day is advised between tests.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

HOW SUPPLIED

R-Gene® 10 is supplied as a 300 mL fill in 500 mL containers.

NDC 0009-0436-24

Exposure of pharmaceutical products to heat should be minimized. Avoid excessive heat. It is recommended that the product be stored at room temperature (25°C); however, brief exposure up to 40°C does not adversely affect the product. Solution that has been frozen must not be used.

Manufactured for
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By
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R-Gene® is a registered trademark of Pharmacia AB.

Directions for Use of I.V. Container

The important feature of this container is that it is a **closed system.** That is, no unfiltered air comes in contact with the solution. The spike is thrust through a solid stopper, the air enters through a bacterial air filter, and only filtered air enters the bottle then or during the infusion. The rubber stopper surface beneath the metal seal is sterile.

A special air-inletting, air-filtering set with a bacterial air filter is required. **No airway needle is needed.**

1. **Use only if solution is clear and seal is intact.** Carefully examine bottle for evidence of damage, e.g., dents or other evidence of damage to metal cap, small cracks, dents in seal, or areas of dried powder on exterior. **Do not administer contents if such damage is found.**

2. Remove tamperproof metal seal and metal disc from bottle to expose rubber stopper, taking care that you do not contaminate the target site of the stopper with fingers, hair, clothing, etc. **Immediately** perform step #3.

3. With shut-off clamp closed, remove sterility protector from spike of administration set and immediately insert set with a quick thrust into center of stopper with bottle upright on table. (Push straight in — don't twist — twisting may cause stopper coring.)

4. Promptly invert bottle to automatically establish fluid level in drip chamber and to check for vacuum by observing rising filtered air bubbles. **Discard bottle if there is no vacuum or if the solution is not clear.**

5. Clear tubing of air. Proceed with infusion.

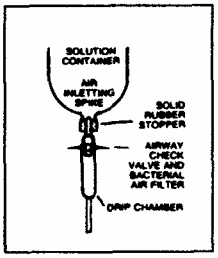
CAUTION: While the top of the rubber stopper is sterile, as soon as the seal and disc are removed the stopper is exposed. The longer the time between removal of the seal and disc and the piercing of the stopper, the greater the chance of contamination of the stopper.

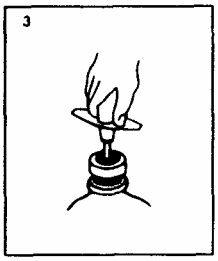
NOTE: When medication is to be added to the bottle:

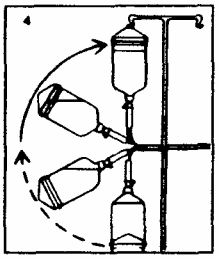
A. See #1 and #2 above.

B. Add medications before attaching administration set. Vacuum should be observed at this point, by sucking in of additive container content, since vacuum may be lost during this procedure and not observable during administration set insertion.

C. If medications have been placed in bottle through stopper, it is recommended that the face of the stopper be swabbed immediately before piercing with administration set.







CONTINUED USE OF SOLUTIONS AND SETS

Procedure differs with every hospital for the length of time solutions and administration sets may be used continuously. Some recommend change of both every 8 hours, others recommend change of both every 24 hours, and others recommend change of solutions every 8 hours and change of sets every 24 hours. The shorter the period of use the less the possibility of multiplication of organisms inadvertently introduced.

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